guidance of how to use a nucleic molecule of at least 15 nucleotide that hybridize to the nucleic acid molecule are claimed.

The Examiner stated that the nucleotide sequence of the prostate specific membrane antigen is over 2000 nucleotide and it would be an undue burden to an artisan in the art to determine hose molecule(s) of at least 15 nucleotide of that specific hybridize as claimed given that molecules of 15 nucleotide have different sequences and would not have expected to hybridize equally to the claimed molecule. The Examiner stated that furthermore, since the specification does not disclose the experimental parameters used for hybridization it would be an undue burden to identify nucleic acid of as least 15 nucleotide which specifically hybridize the nucleic acid molecule encoding the specific antigen.

The Examiner stated that additionally, the specification provides insufficient guidance to those nucleic acid molecules that encode for modifications (i.e. deletions, or additions) to the PSM, nucleic acid molecules which encodes for a product that has the biological activity, and nucleic acid molecule which hybridize conditions to the DNA as set forth in the claimed invention. The Examiner stated that the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of deletions, additions, or modifications broadly encompassed by the claims and the claims broadly encompass a significant number inoperative species. The Examiner stated that the amino acid sequence of a protein determines its structural and functional properties, and the predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and

detailed knowledge of the ways in which the proteins' structure relates to its function. The Examiner stated that however, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation. The Examiner stated that while recombinant and mutagenesis techniques are known, it is not routine in the art to screen for positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity/utility are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure. The Examiner stated that one skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g. multiple deletions. The Examiner stated that the sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins. The Examiner stated that the specification does not support the broad scope of the claims because the specification does not disclose the following:

- the general tolerance to modification and extent of such tolerance;
- specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical;
- what fragments, if any, can be made which retain the biological activity of the inact protein; and
- the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

The Examiner stated that thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and

use the claimed protein in manner reasonably correlated with the scope of the claims broadly including any number of deletions and fragments of any size. The Examiner stated that the scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). The Examiner stated that without such guidance, the changes which can be made in the proteins structure and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

The Examiner stated that protein chemistry is probably one of the most unpredictable areas of biotechnology. The Examiner stated that for example, Kumar et al. teach amino acid variation at a single residue can affect the properties of the function of a peptide. The Examiner stated that Bowie et al. teach at certain positions of a protein, no substitutions or only conservative substitutions are allowed. The Examiner stated that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduce the biological activity of the mitogen (see Lazar et al.). The Examiner stated that these references demonstrates that a even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. The Examiner stated that in view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of derivatives of DNA which encode for a protein (or polypeptide, peptide encompassed in the scope of the claims one skilled in the art would be forced into undue experimentation in order to practice broadly the claimed invention.

The Examiner stated that additionally, the specification provide

insufficient guidance of how to use a "molecule of at least 15 nucleotides" for as broadly recited since:

1) the claimed "molecule of at least 15 nucleotides" is not limited to any "sequence"; and
2) the art as exemplified by US Patent No. 5,538,866 only sets forth "For prostatic cancer, the PSM antigen probe may prove beneficial" (see Column 21, lines 50-59); and a skilled artisan would be forced into undue experimentation to practice the claimed invention.

In response, applicant's respectfully traverse the Examiner's objections. Applicants maintain that one skilled in the art would be able to practice the claimed invention in that once a sequence is known, it is a routine experiment to design an appropriate probe. Applicants also contend that Sambrook, Fritsch and Maniatis (1989) entitled "Molecular Cloning, a Laboratory Manual-Second Edition" describes different probes and different conditions for hybridization. A copy of chapter 11 entitled "synthetic oligonucleotide probes" is attached hereto as **Exhibit A**. Applicants respectfully point out that this manual was published in 1989, which is before applicant's filing date. In particular, applicants point the Examiner's attention to the discussion of hybridization conditions which begins on page 11.46. Applicants respectfully contend that the above remarks obviate the Examiner's objections and respectfully request that the Examiner reconsider and withdraw the objections.

The Examiner stated that the prior rejection of claims 90-99 under 35 U.S.C. §112, first paragraph, for written description is withdrawn in view of applicants amendment.

<u>Rejection Under 35 U.S.C. §112, Second Paragraph</u>

The Examiner rejected claims 90-99 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point

out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner rejected claims 90-99 for using the phrase "specifically hybridizing" since it is not clear what conditions constitute as "specifically hybridizing".

In response, Applicants respectfully traverse the Examiner's objection. Applicants maintain that one skilled in the art would know to use the hybridization conditions set forth in a laboratory manual, such as in Sambrook, Fritsch and Maniatis (1989) entitled "Molecular Cloning, a Laboratory Manual-Second Edition." A copy of the relevant chapter entitled "conditions for hybridization of oligonucleotide probes" is attached hereto and applicants particularly point the Examiner's attention to the section which begins on page 11.45. Applicants maintain that these remarks obviate the Examiner's objections and respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner rejected claims 91, 92, 93, and 95 for being vague and indefinite since it is not clear if the DNA (or RNA) molecule as claimed is referring to the nucleic molecule or at least 15 nucleotides or the molecule encoding the antigen as recited.

In response, Applicants have hereinabove amended the claims. Applicants respectfully contend that the amendment obviates the above objection and respectfully request that the Examiner reconsider and withdraw the rejection.

<u>Rejection Under 35 U.S.C. §102(b)</u>

The Examiner rejected claims 90, 92, 93 and 95 under 35 U.S.C. §102(b) as being anticipated by Solin et al. (Biochmical et. Biophysica, 1048:72-77, 1990).

The Examiner stated that Solin et al. discloses isolated total

RNA form LNCaP (see entire document especially pages 72, 73; and Figure 2). The Examiner stated that it is inherent that the isolated RNA of the prior art encodes the claimed antigen, as the gene encoding the claimed antigen is derived from the same source. The Examiner stated that further the RNA of the prior art is at least 15 nucleotides, capable of hybridizing with an isolated nucleic acid molecule, and complementary.

In response, Applicants respectfully traverse the Examiner's objection. Solin et al. teaches an isolated nucleic acid encoding human prostatic phosphatase (PAP). Yet, Solin et al does not teach the existence of an isolated nucleic acid molecule encoding the prostate specific membrane antigen, the subject of Applicant's claimed invention. Solin et al discloses the total RNA from LNCaP human prostatic cancer cell line. The Examiner contends that this would inherently comprise a nucleic acid encoding a prostate specific membrane antigen. Yet, Applicants claims are directed to an (isolated) nucleic acid molecule. The claims are not directed to a composition. The mixture of total mRNA from LNCaP does not anticipate "an isolated nucleic acid molecule" because the prior art does not teach the isolated nucleic acid molecule of the subject invention. See In re Katz and Strasburger, 201 USPQ 71(CCPA 1979). See Ex Parte Stern, 13 USPQ2d 1379 (BPAI 1987). Copies of these cases are attached hereto as **Exhibit B** and **Exhibit C**, respectively. Applicants contend that these remarks obviate the above objections and respectfully request that the Examiner reconsider and withdraw the rejection of claims 90, 92, 93 and 95.

Rejection Under 35 U.S.C. §102(b)

The Examiner rejected claims 90-95 under 35 U.S.C. §102(b) as being anticipated by Faber et al. (J. Bio. Chem. 266:10743-10749, 6/91).

The Examiner stated that Faber et al. discloses of isolated RNA

and a cDNA library from LNCaP (see entire document especially pages 10745 and 10747). The Examiner stated that it is inherent that the isolated RNA and cDNA of the prior art encodes the claimed antigen as the gene encoding the claimed antigen is derived from the same source. The Examiner stated that further the nucleic acid molecule of the prior art is at least 15 nucleotide, capable of hybridizing with an isolated nucleic acid molecule, and complementary as claimed.

In response, Applicants respectfully traverse the Examiner's objection. Faber et al. teaches an isolated nucleic acid encoding human androgen receptor. Yet, Faber et al does not teach the existence of an (isolated) nucleic acid molecule encoding the prostate specific membrane antigen, the subject of applicant's claimed invention. Faber et al discloses the total RNA from LNCaP human prostatic cancer cell line. The Examiner contends that this would inherently comprise a nucleic acid encoding a prostate specific membrane antigen. Yet, Applicants claims are directed to an (isolated) nucleic acid molecule. The claims are not directed to a composition. The mixture of total mRNA from LNCaP does not anticipate "an isolated nucleic acid molecule" because the prior art does not teach the isolated nucleic acid molecule of the subject invention. See In re Katz and Strasburger, 201 USPQ 71(CCPA 1979). See Ex Parte Stern, 13 USPQ2d 1379 (BPAI 1987). Copies of these cases are attached hereto as **Exhibit B** and **Exhibit C**, respectively. Applicants contend that these remarks obviate the above objections and respectfully request that the Examiner reconsider and withdraw the rejection of claims 90, 92, 93 and 95.

In view of the foregoing remarks, applicants respectfully request that the Examiner reconsider and withdraw the various grounds for objection and rejection and earnestly solicit allowance of the claims now pending in the subject application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

No fee, other than the enclosed $475.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Albert Wai-Kit Chan 11/12/98
Albert Wai-Kit Chan Date
Reg. No. 36,479